Nicotine Polacrilex Gum	Circa Pharmaceuticals
4 mg/piece Chewing Gum	Copiague, NY
ANDA #74-707	Submission Date:
Reviewer: Moo Park	August 14, 1997
Filename:74707A.897	

Review of an Amendment

I. Objective

Review of Circa's amendment involving formulation change. Circa had submitted an acceptable *in vivo* bioequivalence study under fasting conditions comparing its Nicotine Polacrilex Gum, 4 mg/piece, to Marion Merrell Dow's Nicorette^{R} DS, 4 mg/piece (submission date: 7/6/95; review date: 5/2/96).

II. Background

The *in vivo* bioequivalence study conducted by Circa on its Nicotine Polacrilex Gum, 4 mg/piece, lot#RD0965, comparing it to MMD's Nicorette^{R} DS, 4 mg/piece, Lot#TF101A, had been found acceptable (submission date: 7/6/95; review date: 5/2/96).

In this amendment, Circa requested a waiver on its new formulation. Circa found chemical stability problem involving nicotine during accelerated stability study of the original formulation and as a result the new formulation was developed.

III. Comments

1. The applicant has changed the amount of nicotine polacrilex resin from [redacted] mg/piece in the old formulation to [redacted] mg/piece in the new formulation, to take into account the change in the [redacted] factor of nicotine in the resin when the amount of glycerin is [redacted] from [redacted] 10%. The nicotine loading increases from [redacted] The new and old formulations are shown in Table 1. The applicant has

claimed that this is a minor change since the n glycerol constitutes a change in <1% total and there is no change in pH buffering capacity. The drug substance is an adduct of nicotine and a cation exchange resin

Table 1. Comparison of Old and New Formulations

Ingredient	Old Formulation mg/piece	New Formulation mg/piece
Nicotine Polacrilex Glycerinated glycerol) + e	-	(=4 mg nicotine)
Nicotine Polacrilex Glycerinated glycerol) + age	(=4 mg nicotine)	
Sorbitol		
Sodium Carbonate		
Gum base		
Gum Flavor 3945		
Butylated Hydroxytoluene		(
FD&C Color Blend		.
Color Lake Blend		0.1
Total gum weight	960	960.00

2. USP23 requires a drug release test in water. Table 2 shows the results of USP23 release test.

Test method: An accurately weighed quantity of nicotine polacrilex glycerinated resin, equivalent to about 4 mg of

nicotine, was added into a centrifuge tube. The weighing was made for each time point for each formulation. To each tube, of armed to was added. All the sample tubes were shaken and each sample tube was taken out at 1, 2, 5, 10 and 15 minutes for assay for released nicotine.

Results: The release profiles of the new nicotine polacrilex glycerinated resin glycerol) and old nicotine polacrilex glycerinated resin glycerol) were almost identical as shown in Table 2. Both old and new nicotine polacrilex resins showed fast nicotine release and met the USP23 specifications of NLT 70% in 10 minutes.

Table 2. Nicotine Release (%) Profiles

Time, min	New Nicotine Polacrilex resin Lot #3892	Old Nicotine Polacrilex resin Lot #3266B
1	69.1	73.7
2	72.6	74.5
5	77.2	76.7
10	77.2	76.2
15	75.2	76.5

3. The firm should perform a chew-out study using the old and new formulations to evaluate nicotine release under use conditions.

4. Waiver will not be granted until the chew-out study data are reviewed.

IV. Deficiency

The firm should submit results of a chew-out study for the old and new formulations performed under use conditions.

V. Recommendation

The amendment submitted for the formulation change of Circa's Nicotine Polacrilex Gum, 4 mg/piece, involving the use of nicotine polarilex with glycerol instead of nicotine polarilex with glycerol used in the original formulation is incomplete. The firm should submit results of a chew-out study for the old and new formulations conducted under use conditions.

The firm should be informed of the recommendation and deficiency.

/S/

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

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Concur: /S/ Date: 3/30/98

Dale P. Conner, Pharm.D.
Director
Division of Bioequivalence

File history: 1st Draft (3/27/98); Final (3/27/98)

BIOEQUIVALENCY DEFICIENCIES

ANDA/AADA: 74-707 APPLICANT: Circa

DRUG PRODUCT: Nicotine Polacrilex Gum, 4mg/piece

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

It is recommended that you submit results of a chew-out study for the old and new formulations performed under use conditions.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

MAY 2 1996

Nicotine Polacrilex Gum	Circa Pharmaceuticals
4 mg/piece Chewing Gum	Copiague, NY
ANDA #74-707	Submission Date:
Reviewer: Moo Park	July 6, 1995
Filename:74707S.795	March 28, 1996

Review of an In Vivo Bioequivalence Study

I. Objectives

Review of Circa's *in vivo* bioequivalence study under fasting conditions comparing its Nicotine Polacrilex Gum, 4 mg/piece, to Marion Merrell Dow's Nicorette^{R} DS, 4 mg/piece.

II. Background

Nicotine is an agonist at nicotinic receptors in the peripheral and central nervous systems. Nicorette, which contains nicotine bound to an ion exchange resin, is indicated as an adjunct to smoking cessation programs. The nicotine present in Nicorette is released from the resin only during chewing. Patients are advised to chew the gum slowly over a period of 30 minutes. The principal site of absorption in subjects who chew nicotine gum is the oral mucosa. Nicotine is extensively metabolized by the liver and the major metabolites are cotinine and nicotine 1'-N-oxide. About 5% of the dose is excreted in the urine as nicotine and approximately 10% as cotinine in 24 hours. The rate of urinary excretion is increased at lower urinary pH and high urine output. Plasma nicotine and cotinine concentrations of approximately 12 ng/mL and 100 ng/mL respectively, can be expected in subjects who chew 1 piece of gum per hour while abstaining from smoking. Following inhalation or parenteral administration, the plasma half-life of nicotine ranges from 0.5-2 hours. The plasma half-life of cotinine is approximately 19 hours.

Nicotine gum currently is available in two strengths: Nicorette, 2 mg and Nicorette DS, 4 mg. Both products are marketed by Marion Merrell Dow.

III. Study Details

1. Protocol #022-R-03

2. Applicant: Circa Pharmaceuticals, Copiague, NY

3. Study sites:
   Clinical study:

   Analytical:

4. Investigators:
   Principal investigator:

   Analytical investigator:

5. Clinical study dates: 10/23/94-10/31/94

   Assay dates: 11/2/94-11/15/94

6. Study design: Open-label, randomized, two-way crossover design.

7. Subject: The subjects will be healthy males, 19-55 years of age, who are smokers with a habit of smoking 1 to 1 1/2 packs of cigarettes a day, weighing at least 60 kg and who are within 15% of their ideal weight. Thirty (30) healthy male volunteers will be enrolled and dosed, with 24 subjects to complete the study. Dropouts will be replaced prior to analysis with alternate subjects.

8. Product information:

   (a) Test product #1: Circa's Nicotine Polacrilex Gum, 4mg

   Lot #RD 0965

   (b) Reference product: MMD's Nocorette® DS, 4 mg

   Lot #TF101A
   Expiration date: December, 1995

9. Dosing: Before dosing for each period, subjects will undergo a training session with placebo gum provided by Circa Pharmaceuticals, Inc. After a supervised overnight fast, subjects will receive one dose of the assigned chewing gum according to a randomization scheme. While seated, subjects will chew the gum over a period of 30 minutes. The gum will be chewed times every seconds. Rhythm of chewing will be provided by e generation. Subjects will be told to chew the gum times on of the mouth then move the gum to the the mouth. Every seconds the

will sound, prompting the subject to chew always on the side from the previous chew. This process will be repeated for a period of thirty continuous minutes. The subjects will be instructed to at a command given every seconds. Subject compliance will be closely monitored.

10. Food and fluid intake: Subjects will be required to fast overnight 9 hours before dosing and for 4 hours thereafter. Water will not be permitted for 2 hours before and 4 hours after dosing. A standard meal will be provided at 4 hours after dosing and at appropriate times thereafter. During confinement, meal plans will be identical for both periods. The consumption of alcohol or xanthine containing beverages and foods will be prohibited during the study.

11. Housing: From 36 hours before dosing until after the 24 hour blood draw.

12. Washout period: Seven days.

13. Blood samples: Blood samples (mL each) will be collected at 36 hours prior to dosing, time 0 (prior to dosing) and at the following times after dosing: 10, 20, 30, 40, 50 minutes and 1, 1.17, 1.33, 1.5, 1.67, 1.83, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 5, 6, 8, 12, 16 and 24 hours. Plasma samples will be stored at -20^0C or lower, pending assay for nicotine and cotinine levels.

14. IRB and informed consent: Yes

15. Pharmacokinetic and statistical analysis: S A S - G L M procedures were used on AUC_t, AUC_{inf}, C_{max}, T_{max}, K_{el}, $t_{1/2}$ and blood levels at each sampling points. The 90% confidence intervals (CI) were calculated for AUC_t, AUC_{inf} and C_{max}.

Page(s) 2

Contain Trade Secret, Commercial/Confidential Information and are not releasable.

raw data

V. In Vivo Results with Statistical Analysis

Thirty (30) subjects participated in the study and completed the crossover study successfully. Nineteen adverse reactions (7 for test and 12 for reference) from 10 subjects were reported. All were not serious.

The plasma cotinine levels and the PK parameters for cotinine are not presented here because cotinine is not used in the evaluation of bioequivalence.

1. Mean plasma levels

The mean plasma nicotine levels for the test and reference products were comparable as shown in Table 4 and Figure p-1.

Table 4. MEAN PLASMA NICOTINE LEVELS FOR TEST AND REFERENCE PRODUCTS
MEAN1=TEST MEAN2=REFERENCE RMEAN12=TEST/REF RATIO

	MEAN1	SD1	MEAN2	SD2	RMEAN12
TIME HR					
0	0.00	0.00	0.00	0.00	.
0.167	1.52	1.13	1.31	1.01	1.16
0.333	5.91	2.34	5.66	1.78	1.04
0.5	7.73	2.44	7.64	2.56	1.01
0.666	8.83	2.37	8.46	2.78	1.04
0.833	9.44	2.16	9.28	3.04	1.02
1	9.69	3.19	9.20	3.25	1.05
1.167	9.31	3.29	9.21	3.11	1.01
1.333	9.05	3.31	8.31	3.04	1.09
1.5	8.45	3.35	8.10	3.07	1.04
1.666	7.75	3.12	7.83	3.15	0.99
1.833	7.54	3.45	7.44	3.45	1.01
2	6.91	3.25	6.80	3.15	1.02
2.25	6.60	3.49	6.23	2.83	1.06
2.5	5.86	2.92	5.83	2.63	1.01
2.75	5.57	3.09	5.38	2.79	1.03
3	5.10	3.04	5.05	2.79	1.01
3.5	4.36	2.66	4.29	2.46	1.02
4	3.74	2.60	3.69	2.09	1.01
5	2.63	2.39	2.50	1.95	1.05
6	1.61	1.90	1.58	1.76	1.02
8	0.79	1.70	0.65	1.50	1.22
12	0.23	0.98	0.22	0.81	1.05
16	0.12	0.67	0.09	0.49	1.37
24	0.04	0.22	0.04	0.21	1.06

UNIT: PLASMA LEVEL=NG/ML TIME=HRS

2. Pharmacokinetic parameters

The pharmacokinetic parameters, CMAX, AUCT and AUCI, are comparable for the test and reference products as shown in Table 5. The test/reference ratio ranges 1.04-1.06 for the non-transformed parameters and 1.02-1.04 for the log-transformed parameters.

The 90% confidence intervals for the log-transformed CMAX, AUCT and AUCI are all within 80-125% as shown in Table 6.

There was no significant effect observed for period, sequence and treatment.

Table 5. TEST MEAN/REFERENCE MEAN RATIOS (*ANTILOG CONVERSION)
MEAN1=TEST MEAN2=REFERENCE RMEAN12=TEST/REF RATIO

	MEAN1	SD1	MEAN2	SD2	RMEAN12
PARAMETER					
AUCI	40.96	30.35	38.73	26.53	1.06
AUCT	36.13	29.14	34.58	25.49	1.04
CMAX	10.96	3.90	10.53	3.16	1.04
KE	0.34	0.07	0.35	0.07	0.99
LAUCI*	36.08	0.45	34.77	0.41	1.04
LAUCT*	31.25	0.48	30.61	0.43	1.02
LCMAX*	10.45	0.30	10.15	0.27	1.03
THALF	2.15	0.75	2.12	0.73	1.01
TMAX	1.01	0.25	1.00	0.39	1.01

UNIT: AUC=NG HR/ML CMAX=NG/ML TMAX=HR

Table 6. LSMEANS AND 90% CONFIDENCE INTERVALS

	LSMEAN1	LSMEAN2	LOWCI12	UPPCI12
PARAMETER				
AUCI	40.96	38.73	101.59	109.95
AUCT	36.13	34.58	100.21	108.75
CMAX	10.96	10.53	94.51	113.64
LAUCI	36.08	34.77	100.25	107.39
LAUCT	31.25	30.61	98.54	105.73
LCMAX	10.45	10.15	94.97	111.61

3. Residual nicotine in the gums used in the bioequivalence study

Each subjects chewed the gum for 30 minutes. Residual nicotine was measured from the gums collected after 30 minutes' chewing. The results are shown in Table 7. The amount of nicotine release was

comparable for the test and reference products.

Table 7. Residual Nicotine in the gum after 30-minute Chewing

Product	Subject	Residual nicotine Mean, %	%CV
Test	30	22.4	24.3
Reference	30	22.0	24.6

VI. Product Information

1. Formulation

Table 8. Test Formulation

Ingredients	Amount, mg/piece
Gum Base	
Butylated Hydroxytoluene	
Nicotine Polacrilex Glycerinated	
Sorbitol,	
Sodium Carbonate,	
Sorbitol,	
FD&C Color Blend	
	12
Total	960

2. Assay and content uniformity

Assay and content uniformity data are comparable for the test and reference products.

Table 9. Assay and Content Uniformity

Product	Assay, %	Content uniformity, % (%CV)
Test product, Circa RD0965	110.1	110.1 (1.8)
Ref product, MMD TF101A	107.3	106.8 (1.8)

3. Chew-out study: Estimation of nicotine release

Eight subjects participated in the chew-out study, which is a multiple dose crossover design. Each subject chewed a new piece of gum for 5, 10, 20 and 30 minutes. Residual nicotine from the gum was determined and % nicotine released is shown in Table 10. The release pattern of nicotine is comparable for the test and reference products.

Table 10. % Nicotine Released:Chew-Out Study

Time, min	Nicotine released,% Test Product	Nicotine released,% Reference product
5	24.8	26.1
10	51.1	49
20	76.4	72.5
30	84.5	80.9

VII. Comments

1. Thirty (30) subjects participated in the study and completed the crossover study successfully. The applicant assayed nicotine and cotinine in the plasma samples from all 30 subjects. Only nicotine levels and its PK parameters were used in the bioequivalence evaluation. Cotinine data were submitted only for reference. Therefore, cotinine data were not used in the review.

2. Nicotine levels in plasma: The mean plasma nicotine levels for the test and reference products were comparable. The mean

peak nicotine levels were 9-10 ng/mL at approximately 1 hour.

3. The pharmacokinetic parameters, CMAX, AUCT and AUCI, are comparable for the test and reference products. The test/reference ratio ranges 1.04-1.06 for the non-transformed parameters and 1.02-1.04 for the log-transformed parameters. The 90% confidence intervals for the log-transformed CMAX, AUCT and AUCI are all within 80-125%. There was no significant effect observed for period, sequence and treatment.

4. Assay validation: Pre-study and within study validations are acceptable.

5. No clinically significant adverse reaction was reported.

6. Formulation, assay and content uniformity data are acceptable. Batch size of the test product was pieces.

7. Chew-out study showed that 30 minutes' chewing released 85% nicotine for the test product and 81% nicotine for the reference product.

VIII. Deficiency

None.

IX. Recommendations

1. The *in vivo* bioequivalence study conducted by Circa on its Nicotine Polacrilex Gum, 4 mg/piece, lot#RD0965, comparing it to MMD's Nicorette^{R} DS, 4 mg/piece, Lot#TF101A, has been found acceptable. The study demonstrates that Circa's Nicotine Polacrilex Gum, 4 mg/piece, is bioequivalent to the reference product, MMD's Nicorette^{R} DS, 4 mg/piece.

2. The firm has met the *in vivo* bioequivalence study requirements and the application is acceptable.

/S/

Moo Park, Ph.D.
Review Branch III
The Division of Bioequivalence

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Concur: /s/ Date: 5/2/96

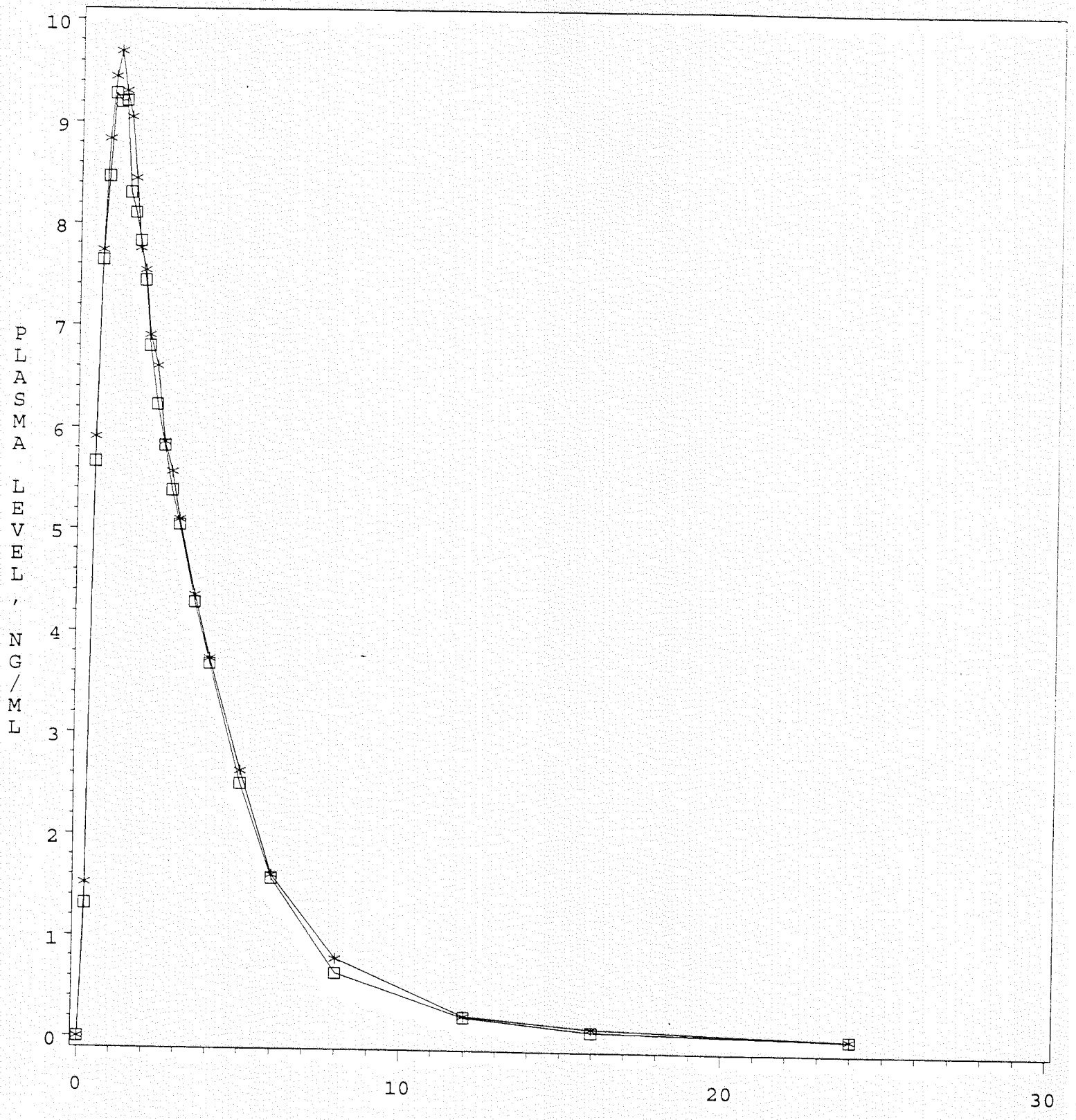
Keith Chan, Ph.D.
Director
Division of Bioequivalence

cc: ANDA # 74-707, HFD-630(OGD), HFD-604(Hare), HFD-658 (Mhatre, Park), HFD-22 (Hooton), HFC-130/JAllen, Drug File

File history: Draft (4/2/96); Final (4/30/96)

FIG P–1. PLASMA NICOTINE LEVELS

NICOTINE POLACRILEX, 4 MG, ANDA #74-707
UNDER FASTING CONDITIONS
DOSE=1 X 4 MG



1=TEST PRODUCT(CIRCA) 2=REFERENCE PRODUCT(MMD)